A response to the Office Action is due March 20, 2002. Accordingly, this R sponse is being timely filed.

By way of this response, claims 1, 8, 24, and 28 have been amended. Accordingly, claims 1-9 and 17-29 are pending.

Applicant thanks and appreciates the Examiner for indicating that the objections to the Declaration are withdrawn, and that the rejections of the claims under 35 U.S.C. § 112, first and second paragraphs are withdrawn in view of the Response filed September 27, 2001.

The only outstanding rejections of the claims are under 35 U.S.C. § 102 (b) (i.e., claims 17-29), and 35 U.S.C. § 103(a) (i.e., claims 1-9). Applicant addresses those rejections herein.

II. The Amended Claims

An "unmarked" and a "marked-up" version of the claims are enclosed herewith. Claim 1 has been amended by inserting the phrase "the step of". Claims 8 and 24 have been amended by replacing "prevent" with "prevention". Claim 28 has been amended by inserting the word "of". The amendments to the claims are formal in nature. No new matter has been added.

III. The Office Action

A) Item 6 of the Office Action - Rejections Under 35 U.S.C. § 102(b)

Claims 17-29 have been rejected as being anticipated by Ciccarelli et al. (1977). The rejection appears to be based on the interpretation that the sentence "[o]ne volume of

undiluted type G antitoxin was mixed with 5 volumes of botulinal toxin types A, B, C, D, E, F, and G ..." (page 844, right column).

Applicant respectfully traverses the rejection, and respectfully submits that Ciccarelli does not teach each and every element recited in the claims, and therefore Ciccarelli does not anticipate the claims.

Claims 17-29 generally recite a composition comprising at least two types of botulinum toxin. Ciccarelli does not teach any single composition that comprises at least two types of botulinum toxin, as discussed below.

To the extent that the rejection over Ciccarelli is based on the interpretation that type G antitoxin is a neurotoxin, and accordingly, that a composition containing type G antitoxin and a botulinum toxin is a composition comprising at least two neurotoxins, Applicant submits that an antitoxin (i.e., type G antitoxin) is **not a neurotoxin**, as indicated in Applicant's September 27, 2001 response. An antitoxin is an antibody that can neutralize a specific toxin. As defined in Webster's New Universal Unabridged Dictionary Deluxe Second Edition, an antitoxin is "a substance found in blood serum and formed in the body to act against a specific toxin." A copy of this definition is annexed herewith as **Exhibit B**.

Accordingly, Ciccarelli's composition of type G antitoxin and another botulinum toxin, such as type A, is not a composition comprising at least two neurotoxins selected from the group consisting of botulinum toxin types A, B, C, D, E, F, and G.

To the extent that the rejection is based on the interpretation that the phrase "5 volumes of botulinal toxin types A, B, C, D, E, F, and G" refers to a single composition comprising seven types of botulinum toxins (i.e., types A, B, C, D, E, F, and G), Applicant respectfully submits that the reference has been mischaracterized in that the

phrase "5 volumes of botulinal toxin types A, B, C, D, E, F, and G" **does not refer to a single composition** comprising the seven types of botulinum toxin.

Applicant respectfully submits that the phrase "5 volumes of botulinal toxin types A, B, C, D, E, F, and G" refers to 5 volumes of one composition having botulinum toxin type A, 5 volumes of one composition having botulinum toxin type B, etc. Thus, the phrase "5 volumes of botulinal toxin types A, B, C, D, E, F, and G" refers to seven different compositions, each composition having one type of botulinum toxin. This interpretation of that phrase is supported by the fact that the very next sentence states "[t]he **mixtures** were incubated" (emphasis added), indicating that a plurality of mixtures (i.e., a mixture is a mixture of one volume of type G antitoxin, and 5 volumes of one type of botulinum toxin) were used. Then, "0.6 ml of **each** [mixture] was injected into each member of a separate mouse pair." (emphasis added). Clearly, if Ciccarelli utilized one mixture comprising type G antitoxin and seven different types of botulinum toxin, they would not have referred to incubating the **mixtures**, and injecting **each** mixture. Furthermore, page 845, right column states that "type G antitoxin . . failed to neutralize 10 to 20 mouse LD_{50} of type A, B, C, D, E, or F toxin." (emphasis added) indicating that the type G antitoxin was separately screened against each type of botulinum toxin, and not screened against a single composition comprising multiple types of botulinum toxins.

Thus, Ciccarelli fails to disclose one composition that comprises at least two types of botulinum toxins as recited in the claims, and therefore, Ciccarelli does not anticipate the claims. As indicated above, an antitoxin is not a neurotoxin (it is an antibody to a neurotoxin), and therefore a composition having an antitoxin and a neurotoxin does not anticipate a claim reciting at least two neurotoxins. Also, the cross-neutralization tests were conducted on mixtures of type G antitoxin and one type of botulinum toxin, not one mixture containing type G antitoxin and multiple types of botulinum toxin. In view of the foregoing, Applicant respectfully submits that the rejection has been overcome, and Applicant respectfully requests the rejection be withdrawn.

In addition, Applicant notes the Examiner's reliance on Pearce et al. (U.S. Patent No. 6,087,327, published July 11, 2000) to support an alleged knowledge in the art that compositions containing mixtures of neurotoxins are used for therapeutic purposes (Office Action, page 3 to page 4). Applicant respectfully disagrees and submits that Pearce et al. is not relevant to establishing the knowledge in the art with respect to the instant invention. The instant application has an effective filing date of June 10, 1993. Pearce has a priority date of 1995, approximately **2 years after** the inventors of the instant application reduced this invention to practice. Thus, the teachings of Pearce do not establish that, as of June 10, 1993, compositions containing at least two neurotoxins could be therapeutic. Instead, Pearce provides post-filing date confirmatory evidence of the patentability of the present invention, e.g., that a composition having more than one type of botulinum toxin has surprising therapeutic effects.

Applicant also respectfully disagrees with the Examiner's reliance on Jankovic et al., to support the art's knowledge of therapeutic uses of compositions containing mixtures of neurotoxins, as discussed below.

B) Item 7 of the Office Action - Rejections Under 35 U.S.C. § 103(a)

Claims 1-9 have been rejected under 35 U.S.C. § 103(a) as allegedly obvious over Jankovic et al. (New England Journal of Medicine, 1991) in view of Ciccarelli et al. (1977). The Office Action states that it would have been obvious "to add the botulinum toxin composition as taught by Ciccarelli et al to the composition of botulinum A used in the method of treating neuromuscular disorders as taught by Jankovic because Jankovic et al teach that patients with antibodies against botulinum toxin A will respond to injections with other botulinum that are immunogenically distinct from type A (p. 1189, 1st column)." (Office Action page 5, last paragraph).

Applicant has considered the rejection and respectfully traverses the rejection.

Jankovic is a review article regarding therapeutic uses of botulinum toxin type A. Jankovic only discloses the use of type A botulinum toxin. Jankovic does not state, or even suggest, that any other type of botulinum toxin can be simultaneously administered in combination with type A, let alone any other type of botulinum toxin. The statement at page 1189, column 1 referred to in the Office Action, "[i]t is likely that patients with antibodies against botulinum toxin will respond to injections with other botulinum toxins that are immunologically distinct from type A", refers to a separate use of another non-type A botulinum toxin. The statement is not referring to simultaneous administration, as recited in the pending claims. Applicant also notes that the statement does not provide a reasonable expectation of success of using other types of botulinum toxin at least due to potential cross-reactivity between antibodies for different botulinum toxins. Thus, Jankovic does not teach or suggest the use of any combination of botulinum toxins to treat patients.

In addition, Applicant respectfully submits that the combination of Jankovic and Ciccarelli fails to make obvious the claimed invention because Ciccarelli does not disclose, or even suggest, a composition that comprises at least two types of botulinum toxin, as discussed above. Ciccarelli does not reveal anything more than the other prior art, namely compositions comprising a single type of botulinum toxin.

Applicant also respectfully submits that one skilled in the art would not be motivated to use the composition of Ciccarelli (i.e., a composition containing type G antitoxin, plus one type of botulinum toxin, as discussed hereinabove) in a therapeutic method as taught by Jankovic because one skilled in the art would recognize the undesirability of unnecessarily administering a composition containing type G antitoxin to a patient when the therapy is based on the administration of a botulinum toxin. Botulinum toxin therapy requires the use of highly pure compositions. The presence of a type G antitoxin would substantially alter the purity of the composition, and thus, one skilled in the art would not be motivated to use such a composition in therapeutic methods. Indeed, it would seem

contraindicated to treat a patient by administering a composition containing a botulinum toxin and an antitoxin.

It also appears that in rejecting the claims based on the combination of Jankovic and Ciccarelli, the teachings of Ciccarelli have been disregarded. The references must be interpreted as a whole, and cannot be picked apart to deprecate an invention (In re Fine, 837 F.2d 1071, 1075, (Fed. Cir. 1988)). As indicated above, Ciccarelli discloses the use of seven separate compositions having a type G antitoxin and one of the seven types of botulinum toxin in a cross-neutralization assay. Cross-neutralization assays are not methods to treat a neuromuscular disorder. At best, one may be motivated to use Ciccarelli's compositions in additional diagnostic methods, and not therapeutic methods. Thus, the teachings of Ciccarelli should not even be combinable with the teachings of Jankovic, and the rejection should be withdrawn.

Applicant also respectfully submits that the present invention has unexpected properties. One important and unexpected advantage of simultaneously administering at least two different types of botulinum toxin is that the "duration of therapeutic activity" can be controlled without having a second toxin administered sequentially, after the first toxin is no longer effective to provide a therapeutic effect. The prior art does not even suggest such an advantage. Indeed, the primary reference, Jankovic, refers to potentially using other immunologically distinct types of botulinum toxin after antibodies to type A have developed.

This advantage was also confirmed after Applicant's invention by Pearce et al. (U.S. Patent No. 6,087,327) that was submitted as post-filing date confirmatory evidence with Applicant's previous response to support the unique and unexpected properties achieved by the present invention.

Accordingly, the therapeutic effects resulting from the simultaneous administration of at least two types of botulinum toxins are uniquely and substantially different from the

effects achieved by separate administration of two or more toxins, and the claims are therefore novel and unobvious over the prior art.

IV. Conclusion

In view of the amendments and remarks herein, Applicant respectfully submits that all of the pending claims are allowable. Notice of which is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, Applicant's undersigned representative invites the Examiner to telephone him at the number provided below.

Respectfully submitted,

Date: 3/20/02

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CERTIFICATE OF MAILING
I hereby certify that this correspondence is being transmitted via facsimile to the Commissioner for Patents in Washington, DC 20231, to fax number 703-308-4242, on or before March 20, 2002.

Jean F. Heuler, paralegal

UNMARKED VERSION OF THE CLAIMS

C1

1. (2x Amended) A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising the step of administering simultaneously to the patient a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G, an amount of each selected neurotoxin being selected to control a duration of therapeutic activity of the administered neurotoxins.

2. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and B.

3. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and C.

4. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and D.

5. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and E.

6. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and F.

7. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and G.

C2

8. (Amend d) The method according to claim 1 wherein the duration of therapeutic activity is suitable for treatment of joint dislocations, relaxation for physical

therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery and for prevention of muscle contractions prior to or after surgery.

9. The method according to claim 1 wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair, treatment of scoliosis and spasm of sphincter muscles.

17. A composition suitable for treating a patient suffering from a neuromuscular disorder or condition, said composition comprising a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G, an amount of each selected neurotoxin being selected to control a duration of therapeutic activity of the neurotoxins.

18. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and B.

19. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and C.

20. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and D.

21. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and E.

22. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and F.

23. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and G.

C3

24. (Amended) The composition according to claim 17 wherein the duration of therapeutic activity is suitable for treatment of joint dislocations, relaxation for physical therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery and for prevention of muscle contractions prior to or after surgery.

25. The composition according to claim 17 wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair, treatment of scoliosis and spasm of sphincter muscles.

26. A composition suitable for treating a patient suffering from a neuromuscular disorder or condition, said composition comprising a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and derivative of G, an amount of each selected neurotoxin being selected to control a duration of therapeutic activity of the neurotoxins.

27. A therapeutic composition comprising a combination of a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F, and G.

C4

28. (Amended) A therapeutic composition comprising a combination of a therapeutically effective amount of botulinum neurotoxin type A and botulinum neurotoxin type B.

29. A therapeutic composition comprising a combination of a therapeutically effective amount of botulinum neurotoxin type A and botulinum neurotoxin type E.

MARKED UP VERSION OF THE CLAIMS

1. (2x Amended) A method of treating a patient suffering from a neuromuscular disorder or condition, said method comprising the step of administering simultaneously to the patient a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G, an amount of each selected neurotoxin being selected to control a duration of therapeutic activity of the administered neurotoxins.

2. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and B.

3. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and C.

4. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and D.

5. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and E.

6. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and F.

7. The method according to claim 1 wherein the selected neurotoxins are botulinum toxin types A and G.

8. (Amended) The method according to claim 1 wherein the duration of therapeutic activity is suitable for treatment of joint dislocations, relaxation for physical

therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery and for ~~prevent~~ prevention of muscle contractions prior to or after surgery.

9. The method according to claim 1 wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair, treatment of scoliosis and spasm of sphincter muscles.

17. A composition suitable for treating a patient suffering from a neuromuscular disorder or condition, said composition comprising a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and G, an amount of each selected neurotoxin being selected to control a duration of therapeutic activity of the neurotoxins.

18. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and B.

19. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and C.

20. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and D.

21. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and E.

22. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and F.

23. The composition according to claim 17 wherein the selected neurotoxins are botulinum toxin types A and G.

24. (Amended) The composition according to claim 17 wherein the duration of therapeutic activity is suitable for treatment of joint dislocations, relaxation for physical therapy, alleviation of muscle spasm, immobilization of a joint undergoing surgery and for ~~prevent~~ prevention of muscle contractions prior to or after surgery.

25. The composition according to claim 17 wherein the duration of therapeutic activity is suitable for treating tendon and ligament alignment repair, treatment of scoliosis and spasm of sphincter muscles.

26. A composition suitable for treating a patient suffering from a neuromuscular disorder or condition, said composition comprising a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F and derivative of G, an amount of each selected neurotoxin being selected to control a duration of therapeutic activity of the neurotoxins.

27. A therapeutic composition comprising a combination of a therapeutically effective amount of at least two neurotoxins selected from a group consisting of botulinum toxin types A, B, C, D, E, F, and G.

28. (Amended) A therapeutic composition comprising a combination of a therapeutically effective amount of botulinum neurotoxin type A and botulinum neurotoxin type B.

29. A therapeutic composition comprising a combination of a therapeutically effective amount of botulinum neurotoxin type A and botulinum neurotoxin type E.

Exhibit A